REMARKS

Status of Claims

Upon entry of this paper, claims 1, 27, 29, 36, 40, 42, 54-59, 101-104, and 108 are amended, and new claim 110 is added.

After entry of this paper, claims 1, 3, 5, 10-11, 14-15, 17-19, 21-24, 27-30, and 33-43, 48-59, 61-63, and 86-94, and 101-110 are pending. Of the pending claims, claims 19, 21-24, 27-30, 33-39, and 41 (corresponding to Groups II and III in the Restriction Requirement of July 25, 2008) are withdrawn by the Examiner.

Applicants reserve the right to pursue any canceled subject matter in one or more related applications.

Support for Amendments

Claims 1, 40, and 42 are amended to recite a "cross-linked and sterile" haemostatic composition. Claim 1 is further amended to replace "stabilized" with "cross-linked and sterilized" with reference to the action of dry heat at 110-200°C. Claims 101 and 103 are amended to recite a "sterile" haemostatic composition. Support for cross-linked and sterile compositions can be found throughout the specification as filed, for example at page 24, lines 17-19, and page 25, lines 8-9.

Claims 1, 27, 29, 36, 40, 42, 54-59, 101-104, and 108 are amended to remove an extra comma as suggested by the Office Action. Claims 103 and 104 are amended to replace British with American spelling for the term "stabilized."

Claim 110 is added as an embodiment of the claimed composition depending from claim 1. Support for the time of the dry heat treatment can be found at throughout the specification as filed, for example, at page 15, line 37, and page 19, lines 1-3.

No new matter is entered.

Entry of Amendments After "Final" Rejection

Applicants request entry of the amendments after "final" rejection, as the amendments raise no new issues for consideration and/or place the claims in better condition for allowance or appeal. Specifically, the correction of typographical matters (i.e., the removal of a comma as suggested by the Office Action and replacement of British spelling with American spelling) raises no new issues for consideration. Claims 1, 40, and 42 are amended to recite "cross-linked" which was previously presented at least in claims 43, 61, and 101, thus raising no new issues for consideration. Claims 1, 40, 42, 101, and 103 are amended to include an aspect of sterilization which was previously presented in claim 34, thus raising no new issues for consideration. In addition, Claim 110 is added as an embodiment of the claimed composition depending from and entirely within claim 1, thus raising no new issues for consideration.

Objection

The Office Action objects to claims 40, 42, 54-59, and 101-109 for placement of a comma. Upon entry of the amendment, the comma is removed. Applicants respectfully request withdrawal of the objection.

Rejection Under 35 U.S.C. §102(b)

The Office Action rejects claims 1, 3, 5, 10, 11, 17, 40, 42, 43, 51, 57, 61-63, 86, 89, 92, 95, and 98 under 35 U.S.C. §102(b) as being anticipated by Choi et al (J. Biomed. Mater. Res.). Applicants understand the rejection of claims 95 and 98 is moot as the claims are not pending, and that the mention of claim 47 at page 4, line 11 of the Office Action is similarly moot for the same reason. With respect to the remaining claims, Applicants respectfully traverse the rejection for at least the reason that Choi does not disclose the currently claimed features.

The Federal Circuit has held that "[A]nticipation under § 102 can be found only when the reference discloses exactly what is claimed and that where there are differences between the reference disclosure and the claim, the rejection must be based on § 103 which takes differences into account." *Titanium Metals Corp. v. Banner*, 778 F.2d 775 (Fed. Cir. 1985).

With regard to claims 1, 40, and 42, and the claims dependent therefrom, the claims recite cross-linked and sterile haemostatic compositions comprising gelatin and hyaluronic acid or a derivative of hyaluronic acid, where the haemostatic composition is cross-linked with dry heat at 110-200°C. Choi fails to anticipate the claims because Choi fails to disclose cross-linked and sterile gelatin and hyaluronic acid treated with dry heat, let alone treatment with dry heat at a temperature 110-200°C. In other words, the composition of Choi cannot be the same as the claimed composition because Choi does not teach a one-step process for obtaining a sterile and cross-linked haemostatic composition with dry heat.

While the Office Action asserts on page 3 that Choi teaches physical cross-linking by thermal heating, this is not actually the case. Choi actually mentions physical cross-linking by thermal heating in the context of gelatin only (see Choi, p. 631, last paragraph). In fact, Choi

discloses compositions that are cross-linked by a chemical agent such as EDC (see Choi, Materials and Methods, p. 632).

As the compositions taught by Choi are formed in a completely different manner from the claimed compositions, the compositions would inherently be different. There is no technical basis for the conclusion in the Office Action that the compositions of Choi and the instantly claimed compositions are "substantially similar, if not the same" as stated in the Office Action at page 4, line 5. Rather, the composition of Choi and the instantly claimed compositions are made by entirely different procedures, thus imparting different characteristics to the resulting compositions. Therefore, claims 1, 40, and 42 (and the claims dependent therefrom) are novel over Choi.

Rejection Under 35 U.S.C. §103(a)

The Office Action rejects claims 1, 3, 5, 10, 11, 14, 15, 17-18, 40, 42-43, 48-59, 61-63, 86-99, and 101-109 under 35 U.S.C. §103(a) as being obvious in view of the combination of Choi et al (J. Biomed. Mater. Res.), Della Valle et al (US Patent No. 4,851,521), Moore et al (US Patent No. 3,678,933), and Cascone et al (J. Mat. Sci., 1994). Applicants understand the rejection of claims 95-99 is moot as the claims are not pending.

U.S. case law holds that a proper obviousness inquiry requires four factual inquiries: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary consideration. See *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966). Although the Supreme Court in *KSR* recently rejected a rigid application of the "teaching, suggestion, motivation" test, the Court did recognize that a showing of "teaching,

suggestion, or motivation " to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). See *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 419 (2007). The Court further noted that an analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit, and that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, at 418.

Applicants respectfully traverse the rejection of the pending claims for at least the reasons that Choi fails to teach the required elements, the secondary references Della Valle and Moore fail to remedy the deficiencies of Choi, and the secondary reference Cascone is not properly combinable with Choi.

Choi Fails To Teach The Claimed Elements

The Office Action holds that Choi anticipates claims 1, 3, 5, 10, 11, 17, 40, 42, 43, 51, 57, 61-63, 86, 89, and 92, thus rendering them obvious. Applicants respectfully disagree for at least the reason that addition of the feature "sterile" to the independent claims renders all claims of the present invention non-obvious over the primary reference. Choi does not teach or suggest a one-step process for cross-linking and sterilization to obtain a sterile and cross-linked haemostatic composition as claimed.

Cross-linked and sterile haemostatic compositions according to the invention can be conveniently prepared in a one-step process, rendering additional steps for sterilization and/or removal of toxins unnecessary. By comparison, the sponge disclosed in Choi requires

sterilization with ethylene oxide (EO) gas for 6 hours, followed by aeration for at least 24 hours (page 632-633). In addition, ethylene oxide is a carcinogenic substance, making its use in medical compositions problematic. The problem of toxicity of ethylene oxide is compounded by the fact that the chemical cross-linking agents as taught by Choi are also toxic (see Choi, p. 632, col. 1).

As the compositions taught by Choi are formed in a completely different manner from the claimed compositions, the compositions would inherently have different properties. There is no technical basis for the conclusion in the Office Action that the compositions of Choi and the instantly claimed compositions are "substantially similar, if not the same" as stated in the Office Action at page 4, line 5. Rather, the composition of Choi and the instantly claimed compositions are made by entirely different procedures, thus imparting different characteristics to the resulting compositions, with no suggestion in Choi of modifications that would lead to the presently claimed compositions. Therefore, claims 1, 40, and 42 (and the dependent claims) are not rendered obvious by Choi.

The Secondary References Della Valle and Moore Fail to Remedy the Deficiencies of Choi

Della Valle is cited by the Office Action with respect to the limitation of a haemostatic sponge comprising an ester of HA according to claim 3, asserting that "Della Valle et al. teach esters of HA or a salt thereof being used for medical use such as spongy materials (Example 42 in col. 50)" (Office Action, p. 6, lines 20-21). However, Della Valle fails to remedy the deficiencies of Choi with respect to the independent claims and the requirement of cross-linked and sterile haemostatic compositions.

Moore is cited by the Office Action with respect to the limitation wherein at least one of the surfaces of the haemostatic sponge is covered by a top sheet according to claim 14, asserting that it is well-known in the art "that a surgical dressing or sponge employs a plastic film as a cover, and also Moore et al. teach the use of think plastic film as a cover of surgical dressing or sponge (col. 1, lines 43-55)" (Office Action, p. 7, lines 1-3). However, Moore fails to remedy the deficiencies of Choi with respect to the independent claims and the requirement of cross-linked and sterile haemostatic compositions.

The Secondary Reference Cascone Is Not Properly Combinable with Choi

Cascone is newly cited with respect to teaching a sponge containing polyacrylic acid (a synthetic polymer) and HA, being crosslinked by thermal heating at 130°C (under vacuum), where the sponge may contain 20-60% HA. Asserting that Choi teaches the thermal crosslinking of gelatin by itself, and Cascone teaches the thermal crosslinking of sponges comprising HA, the Office Action concludes that it would have been obvious "to try the thermal crosslinking method as taught by Choi et al. and Cascone et al. for the composition of Choi et al. and the resulting composition would not comprise a chemical cross-linking agent or residues thereof" (Office Action, p. 9, lines 12-15). In other words, the Office Action proposes that "thermal crosslinking is considered one of predictable solutions known in the art for cross-linking HA and gelatin of Choi et al." (Office Action, p. 9, lines 16-19).

Applicants respectfully traverse the combination of Cascone with Choi for at least the reasons that 1) there is no motivation to modify the compositions of Choi with the process of Cascone; 2) the teachings of Cascone and Choi are directed to different technical problems, and therefore not properly combinable; and 3) there is no reasonable expectation of success in

applying the process of Cascone to the compositions of Choi, and the art is unpredictable regarding the temperature stability of HA.

As discussed above, the Supreme Court in *KSR* noted that an analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit, and that "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, at 418. The Supreme Court pointedly noted that, consistent with a broad body of patent law, "**a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art**." *KSR*, at 418 (emphasis added).

In the present case, there is no objective reason to directly combine the sponge of Choi (a cross-linked composition) with the teachings of Cascone (physical cross-linking by heat treatment) since cross-linking of the sponge of Choi has already been achieved by chemical means. In addition, Choi nowhere teaches, motivates or otherwise suggests that cross-linking of the composition could or should be performed by other means than by the use of a chemical cross-linker. Choi specifically teaches the use of "a minimally toxic" cross-linking agent. See p. 632, col. 1. Choi further teaches that very low concentrations of EDC are sufficient to cross-link the composition. See p. 635, col. 1. Collectively, Choi thus teaches that the use of a minimally toxic chemical cross-linker in very low concentrations is sufficient to cross-link the composition. Importantly, Choi nowhere suggests that a gelatin sponge comprising hyaluronic acid could or should be cross-linked by other means than by the use of a chemical cross-linker.

In addition, Cascone is concerned with the solution of a different technical problem, which is drug delivery, rather than the technical problem of the present invention, which is haemostasis. As there is no motivation provided in Choi to look for cross-linking methods at all

since cross-linking has already been achieved by chemical means, there is absolutely no reason to look for alternative cross-linking methods in a completely different technical field.

It is a well-established principle of patent law that in evaluating obviousness, the claimed invention as a whole must be considered. See, for example, *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782 (Fed. Cir. 1983). See also MPEP 2141.02 for the USPTO's guidance on the cited cases. The Office Action fails to consider the invention as a whole, or to properly consider the cited references in the context of the "scope and contents of the prior art" as required for a proper obviousness analysis. A proper analysis would find that it simply makes no sense to take the crosslinked sponge of Choi and thermally re-crosslink it according to the process of Cascone.

Moreover, it is also an established principle of patent law that a reasonable expectation of success is required for the combination of references to be proper. A rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. See *KSR* at 416 ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.")

To arrive at the present invention by modification of the composition of by applying the teachings of Cascone, one must, as a first step, omit the cross-linking step as taught by Choi without any motivation to do so, and then, as a second step, apply the teachings of Cascone to cross-link the composition, *i.e.* heat the composition at "130°C under vacuum for 24 hours." However, there is nothing in the prior art to suggest that such a treatment for such a length of

time is compatible with the claimed compositions. In other words, the time frame taught for the thermal treatment of Cascone of 24 hours significantly exceeds the time frame for heat treatment as taught by the specification of the present invention, which is 15 minutes to 6 hours (see claim 110).

Cascone teaches a composition comprising hyaluronic acid and a synthetic polymer. Notably, Cascone does not teach a composition comprising gelatin. There is no reason to think that a composition of natural components such as gelatin and hyaluronic acid will react in the same way (i.e. become stabilized or cross-linked) as a composition comprising synthetic polymers according to Cascone. Nor is it obvious that the composition of the present invention can even tolerate the heat treatment as taught by Cascone, which is intended for a partially synthetic composition. Furthermore, the heat treatment as taught by Cascone must be modified to arrive at the present invention by omission of vacuum and heating for a different time frame. In view of the many differences between Cascone and Choi, the Office Action has failed to provide any reason why one of ordinary skill in the art would look to Cascone for any teachings on modifications that could be made to Choi to arrive at the present invention. Absent such reasons, the Office Action can only arrive at the combination of Cascone and Choi through improper hindsight reconstruction using Applicant's own invention.

Applicants respectfully request withdrawal of the rejection for at least the reasons as discussed above.

Lack of Predictability

In addition to the deficiencies of the cited art in supporting a prima facie case of obviousness, there is uncertainty in the art concerning the heat stability of hyaluronic acid. The specification of the present invention specifically teaches that HA is unstable at high temperatures and that it was a surprise to the inventors that a composition comprising HA was active even though it had been treated with dry heat at 110-200°C (page 18, lines 29-32). For further evidence, see Min et al. ("Molecular Weight Changes of Sodium Hyaluronate Powder and Solution by Heat Treatment," Matrix Biology Institute, Proceedings of Hyaluronan, Oct. 11-16, 2003; copy enclosed), which teaches that heat treatment leads to degradation of HA, i.e. heat treatment leads to a significant reduction in the molecular weight of HA. Min teaches an optimal temperature of 70°C (page 3) for heat treatment of a solution of hyaluronic acid, and teaches away from using temperatures higher than 70°C:

> We tested for various temperatures from 70 to 130°C (data are not shown), but could not get consistent results.

(Min, p. 3). Moreover, even in 2009, the general opinion is that HA is highly unstable at temperatures above 60°C. See Fan et al. (US Published Application 2009/0087569), which teaches that "HA is very unstable in conditions that temperature higher than 60° C" (page 1, paragraph [0003]). Fan further teaches that

> At present there are a great deal researchers trying to modify hyaluronic acid in order to expand its use in the medical field, with most of them applying chemical methods as cross-linking or esterificating manœuvers to improve physical strength or reduce decomposition speed in vivo.

(Fan, page 1, paragraph [0006]). Fan provides further evidence that even as of 2009, cross-linking of HA was preferably performed by chemical methods, i.e. by the use of chemical cross-linkers due to HA being considered highly unstable at high temperatures.

Applicants submit that the argument according to the Office Action that "thermal crosslinking is considered one of predictable solutions known in the art for cross-linking HA" is not sustainable when the state of the art is considered. Therefore, it is highly unlikely that a person of ordinary skill in the art would have been motivated to try heat treatment for cross-linking a composition comprising HA at the time the present invention was made.

Evidence of Unexpected Results

Applicants submit that the present invention is patentable over the cited art in view of unexpected results in obtaining a cross-linked and sterile haemostatic composition according to the claims. Specifically, the claimed haemostatic composition (with pro-coagulant properties) is surprising in view of the prior art teachings with regard to anti-coagulant compositions containing HA. For example, Yannas (US Patent 4,280,954) teaches compositions comprising HA and the other species with anti-coagulant properties which are compatible with blood. Examples 12 and 13 of Yannas show that HA-collagen composites fail to exhibit significant differences in whole blood clotting time (WBCT) compared to collagen itself (i.e. 25 ± 5 min. for collagen versus 21.5 ± 2 min. for collagen-HA in Table VIII). These data demonstrate that collagen-HA is comparable to collagen alone in reducing whole blood clotting time under the conditions specified by Yannas, and therefore would not suggest the use of HA in a pro-clotting haemostatic combination.

Indeed, the data presented by Yannas highlight the surprising discovery that compositions comprising gelatin and HA according to the present invention possess a pro-coagulant effect. Even more surprising is the degree of pro-coagulant effect shown by the present invention. For instance, Example 6 of the present application shows that gelatin sponges with HA reduce bleeding intensity more than gelatin sponges without HA, i.e., gelatin powder with 10% HA reduces bleeding 1.28 times better than gelatin powder alone (Table on page 32, S3 versus S2), while the gelatin sponge with 30% HA reduces bleeding 5.2 times better than the gelatin sponge without HA (Table on page 32, S4 versus S1). As such, the present specification provides evidence of unexpected results.

Accordingly, for at least the reasons provided above, Applicants submit that none of the cited references, whether taken alone or in combination, render the claimed invention unpatentable. Having distinguished the independent claims from the art of record, Applicants submit that the dependent claims are patentable for at least the same reasons. However, Applicants reserve the right to separately address the patentability of each dependent claim in the future should that become necessary.

CONCLUSION

Applicants respectfully submit that the instant application is in condition for allowance. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided.

AUTHORIZATION

The Commissioner is hereby authorized to charge any fees which may be required for this amendment, or credit any overpayment to Deposit Account No. **50-3732**, Order No. **13323.105005**. Furthermore, in the event that an extension of time is required, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to the above-noted Deposit Account No. **50-3732** and Order No. **13323.105005**.

Respectfully submitted,
KING & SPALDING, L.L.P.

Dated: December 23, 2009 By: /michael willis/
Jonathan D. Ball / Michael A. Willis
Reg. No. 59,928 / Reg. No. 53,913

KING & SPALDING, L.L.P.
1185 Avenue of the Americas
New York, New York 10036-4003
(212) 556-2115 (212) 556-2222 (Fax)